Neurological, Cognitive, and Behavioral Disorders during COVID-19: The Nitric Oxide Track

To the Editor: Coronavirus disease 2019 (COVID-19) exhibits a wide range of clinical signs, especially in older adults.[1] Alkeridy et al recently reported an interesting case of delirium with lower limb sensorimotor disorders in a 73-year-old man with otherwise asymptomatic COVID-19.[1] The mechanism proposed by the authors was based on the invasion of the nervous system by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, as previously described in a COVID-19 case with encephalitis.[2] Although acknowledging the value of this assumption, we discuss here the likely role of a third player, namely nitric oxide (NO), to explain the onset of neurocognitive disorders in patients with COVID-19.

NO, originally known as an endothelium-derived relaxing factor, is a gaseous membrane-soluble neurotransmitter synthesized endogenously from L-arginine, oxygen, and nicotinamide adenine dinucleotide phosphate by various nitric oxide synthase enzymes.[3-5] Studies in experimental animals have well documented the synthesis of NO in the brain and its role in a variety of neuronal functions including learning and memory processes or locomotor activity.[3]

Although it plays an important role in cell signaling in the brain, NO was described as an "unconventional" neurotransmitter. Indeed, it is neither stored in synaptic vesicles nor released upon membrane depolarization; it is directly released upon synthesis.[4] Also, NO does not mediate its action by binding to some membrane-associated receptors, but it diffuses from neuron to neuron to act on intracellular components.[4] NO functions as a neurotransmitter by stimulating soluble guanylyl cyclase to form a second messenger molecule, cyclic guanosine monophosphate (cGMP), in target cells. The cyclic nucleotide cGMP relaxes vascular smooth muscles with consequent vasodilation and increased blood flow. Increased intracellular cGMP level was shown to contribute to excessive neuron excitability and locomotor activity.[6] The decrease in NO concentrations in the brain was consistently found to induce cognitive and behavioral disorders in various experimental animals.[5]

On this basis, we propose that some of the neurological signs in patients with COVID-19 are associated with the virus-induced decrease in NO levels in the brain. The production of NO is tightly linked to the renin-angiotensin system (RAS), precisely targeted by SARS-CoV-2[7] that was described to overactivate the RAS by interacting, via its spike (S) glycoprotein, with the metallopeptidase angiotensin-converting enzyme 2 (ACE2) receptor,[7] expressed at the surface of numerous cell types including cerebral neurons.[8]

In RAS, angiotensin II, by acting on the vasoconstrictor type 1 angiotensin II receptor (AT_1R), reportedly diminishes the production of NO,[9] leading to an expected decrease in NO concentrations in the brain during COVID-19, which needs to be compensated to prevent neurological cognitive and behavioral disorders. Because NO is basically too reactive (with a very short half-life of 5 seconds) to constitute an appropriate therapeutic target, a strategy would be to counterbalance RAS overactivation and thus maintain the appropriate NO levels in the nervous system. Interestingly, previous work to increase NO concentrations in the brain with specific agents known to elevate NO production was found to improve memory in experimental animals.[5]

In human COVID-19, proposed chemotherapeutic drugs to limit/counterbalance the overactivation of RAS could be ACE inhibitors (to prevent the production of angiotensin II from angiotensin I), blockers/antagonists of AT_1R such as losartan and derivatives, and also some natural candidate peptide drugs that belong to the so-called counterregulatory RAS (i.e., angiotensin 1–7, angiotensin 1–9, alamandine, angiotensin A, and/or angiotensin IV).[10] All these molecules are expected to counteract the SARS-CoV-2-induced overactivation of RAS, to maintain NO production, and to reverse, to some extent, the associated neurological cognitive and behavioral disorders in COVID-19.

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REFERENCES

1. Alkeridy WA, Almaghlouth I, Alrashed R, et al. A unique presentation of delirium in a patient with otherwise asymptomatic COVID-19. J Am Geriatr Soc. 2020;10.1111. https://doi.org/10.1111/jgs.16536.
2. Zhou L, Zhang M, Gao J, Wang J. Sars-Cov-2: underestimated damage to nervous system. Travel Med Infect Dis. 2020;101642. https://doi.org/10.1016/j.tmaid.2020.101642.
3. Susswein AJ, Katzoff A, Miller N, Hurwitz I. Nitric oxide and memory. Neuroscientist. 2004;10:153-162.
4. Garthwaite J, Boulton CL. Nitric oxide signaling in the nervous system. Annu Rev Physiol. 1995;57:683-706.
5. Paul V, Ekambaram P. Involvement of nitric oxide in learning & memory processes. Indian J Med Res. 2011;133:471-478.
6. Tseng K, Caballero A, Dec A, et al. Inhibition of striatal soluble guanylate cyclase-cGMP signaling reverses basal ganglia dysfunction and akinesia in experimental parkinsonism. PLoS One. 2011;6:e27187.
7. Cao Z, Wu Y, Faucon E, Sabatier JM. SARS-CoV-2 & Covid-19: key-roles of the 'renin-angiotensin' system/vitamin D impacting drug and vaccine developments. Infect Disord Drug Targets. 2020;20:1.
8. Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol. 2007;292:R373-R381.
9. Dasgupta C, Zhang L. Angiotensin II receptors and drug discovery in cardiovascular disease. Drug Discov Today. 2011;16:22-34.
10. Annweiler C, Cao Z, Wu Y, et al. Counter-regulatory 'Renin-Angiotensin' System-based candidate drugs to treat COVID-19 diseases in SARS-CoV-2-infected patients. Infect Disord Drug Targets. 2020. https://doi.org/10.2174/1871526520666200518073329.